**UNITED STATES DEPARTMENT OF COMMERCE**
**Patent and Trademark Office**
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, DC 20231

| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. |
|---|---|---|---|
| 08/808,827 | 02/28/97 | GUNZBURG W | GSF97-01A |

HM11/0316

DAVID E BROOK
HAMILTON BROOK SMITH & REYNOLDS
TWO MILITIA DRIVE
LEXINGTON MA 02173

| EXAMINER | |
|---|---|
| BRUSCA, J | |
| **ART UNIT** | **PAPER NUMBER** |
| 1636 | |

DATE MAILED: 03/16/98

**Please find below and/or attached an Office communication concerning this application or proceeding.**

**Commissioner of Patents and Trademarks**



☆U.S.GOVERNMENT PRINTING OFFICE 1995-319-826

| Office Action Summary | Application No. 08/808,827 | Applicant(s) Gunzburg et al. |
|---|---|---|
| | Examiner John S. Brusca | Group Art Unit 1636 |

☐ Responsive to communication(s) filed on _____ .

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

**Disposition of Claims**

☒ Claim(s) 1-27 is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) 1-27 is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

**Application Papers**

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☒ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. § 119**

☒ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☒ None of the CERTIFIED copies of the priority documents have been

☒ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____ .

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

**Attachment(s)**

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). 6, 7

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

*--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---*

## DETAILED ACTION

1. The group and or Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1636.

2. The Computer Readable Form of the sequence listing filed 5/19/97 has been entered without error.

### *Priority*

3. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 120 as follows:

> An application in which the benefits of an earlier application are desired must be copending with the prior application or with an application similarly entitled to the benefit of the filing date of the prior application.

The Applicants have claimed priority to International Application PCT/EP95/03445. In order for the claimed PCT application to be copending with the instant application, the claimed PCT application must have entered Chapter 2 examination, because the instant application was filed after the 20 month deadline for Chapter 1 prosecution in the claimed PCT application, and the claimed PCT application would have been abandoned prior to the filing date of the instant application without entry to Chapter 2 examination which allows for a 30 month deadline after the claimed priority date before abandonment or filing a national stage

application. The Applicants are requested to provide a copy of the Demand for the claimed PCT/EP95/03445 application to establish priority under 35 U.S.C. § 120.

4. Acknowledgment is made of applicant's claim for foreign priority based on an International application filed on 9/1/95. It is noted, however, that applicant has not filed a certified copy of the International application as required by 35 U.S.C. 119(b).

5. Acknowledgment is made of applicant's claim for foreign priority based on an application filed in Denmark on 9/2/94. It is noted, however, that applicant has not filed a certified copy of the foreign application as required by 35 U.S.C. 119(b).

### *Drawings*

6. This application has been filed with informal drawings which are acceptable for examination purposes only. Formal drawings will be required when the application is allowed.

### *Specification*

7. The disclosure is objected to because of the following informalities:

On page 17, line 6 the specification recites "advance" and should be amended to recite "advantage".

Appropriate correction is required.

### *Claim Rejections - 35 USC § 112*

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 1-27 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for retroviral vectors which retain the inverted repeat (att) site in the U3 region of the long terminal repeat (LTR), does not reasonably provide enablement for retroviral vectors that delete the entire U3 region. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

In *In re Wands* (8 USPQ2d 1400 (CAFC 1988)) the CAFC considered the issue of enablement in molecular biology. The CAFC summarized eight factors to be considered in a determination of "undue experimentation". These factors include: (a) the quantity of experimentation necessary; (b) the amount of direction or guidance presented; (c) the presence or absence of working examples; (d) the nature of the invention; (e) the state of the prior art; (f) the relative skill of those in the art; (g) the predictability of the art; and (h) the breadth of the claims.

In considering the factors for the instant claims:

a) In order to practice the claimed invention one of skill in the art must use a retroviral vector that lacks the entire U3 region of the LTR. For the reasons discussed below, such a vector would fail to integrate to form a provirus, resulting in an inoperative vector.

b) The specification provides general guidance on page 16 to delete the region of the LTR that is required for integration.

c) The specification provides a working example of a retroviral vector in which the U3 region is deleted and an artificial inverted repeat site is restored by use of PCR primers that contain an inverted repeat sequence (see page 20 and Figs. 4 and 17).

d) The invention is drawn to a retroviral vector that contains a deletion of the entire U3 region.

e) Panganiban et al. '83 shows the ends of LTRs of retroviruses contain a short inverted repeat of from 5 to 13 base pairs. Panganiban et al. '83 shows in figure 2 retroviral constructs in which the inverted repeat region of the U3 region is deleted. Mutant 60B-150 contains a deletion of part of the inverted repeat region but retains other regions surrounding the inverted repeat region of the U3 region such as the polypurine tract and the 42 base pair repeat region important for promoter activity of the LTR. In figure 7, Panganiban et al. '83 summarize the effect of the 60B-150 mutant by showing that the mutant fails to integrate in the host cell chromosome to form a provirus, that the levels of unintegrated virus are reduced 25 fold over wild type virus, and that the levels of virus production are reduced by a factor of 1000 relative to wild type virus. Although Panganiban et al. '83 states on page 156 that

deletion of the inverted repeat region does not prevent virus production, figure 7 establishes that failure to integrate correlates with a dramatic reduction in viral replication.

f) The skill of those in the art of molecular biology is high.

g) It is predictable that retroviral vectors that lack the inverted repeat (att) site in the 3' U3 LTR will produce viral genomes in which both LTR regions lack the att site in the U3 region as discussed in the instant application on page 14 and figure 3. It is predictable that a retroviral vector that lacks an att site will not integrate into the host chromosome, and will replicate poorly.

h) The claims are broad in that they read on retroviral vectors that cannot integrate into the host genome.

The skilled practitioner would first turn to the instant specification to practice the full scope of the claimed invention. However, the instant specification provides no specific guidance for making or using a retroviral vector that lacks the att site, and provides a working example in which the att site has been deliberately designed into the primers used to construct the working example. As such, the skilled practitioner would turn to the prior art for such guidance. However, Panganiban et al. '83 shows that deletion of the att site from the U3 region results in a retroviral vector that replicates poorly. Finally, said practitioner would turn to trial and error experimentation to use a retroviral vector that lacks the entire U3 region without a reasonable expectation of success. Such represents undue experimentation.

10. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

11. Claims 1-27 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

12. Claims 1-27 are indefinite for recitation of the phrase "capable of". It is not clear if the claims are drawn to a latent property or a property that requires an additional agent for expression. The claims should be amended to distinctly recite the claimed properties using positive language.

13. Claims 17-24, 26, and 27 are indefinite for recitation of the term "system" because it is not clear whether the claims are drawn to a method or a kit. The rejection would be overcome by amending the claims to recite "kit".

14. Claim 13 recites the limitation "said coding sequences for a retroviral protein". There is insufficient antecedent basis for this limitation in the claim.

15. Claims 20 and 21 are indefinite for recitation of the phrase "in vitro and in vivo" because it is not clear how the method can be performed on both types of cells at the same time and because the phrases "in vitro" and "in vivo" are imprecise terms in the art that may read on cell-free reactions, infection of cultured cells of an animal, and infection of animals. The rejection would be overcome by amending claim 20 to recite "that consist of cells of a human or an animal, or isolated cultured cells of a human or an animal".

16. Claim 27 is indefinite for recitation of the phrase "in vitro and in vivo"because it is not clear how the method can be performed on both types of cells at the same time and because the phrases "in vitro" and "in vivo" are imprecise terms in the art that may read on cell-free reactions, infection of cultured cells of an animal, and infection of animals. The rejection would be overcome by amending claim 27 to recite "that consist of cells of a human or an animal, or isolated cultured cells of a human or an animal".

17. Claims 7, 11 and 12 are indefinite for recitation of the phrase "one or more elements of" because the members of the Markush group are not clearly defined. The rejection would be overcome by amending claims 11 and 12 to delete the phrase. Claims 7, 11, and 12 may be amended to conclude with the phrase "or combinations thereof" if the Applicant so desires.

18. Claim 9 is indefinite for recitation of the phrase "selected from at least one element of the group consisting of a long terminal repeat region" because the members of the Markush group are not clearly defined and because it is not clear if all members of the group are long terminal repeat regions. The rejection would be overcome by amending claims 11 and 12 to recite "derived from a retrovirus selected from the group consisting of'.

19. Claim 12 is indefinite because a comma does not appear after the phrase "alcohol dehydrogenase gene" which results in an indefinite member of the recited group.

20. Claim 19 is indefinite because a comma does not appear after the phrase "PA317" which results in an indefinite member of the recited group.

21. For the purpose of examination, the claims have been assumed to incorporate the

suggested amendments.

*Claim Rejections - 35 USC § 102*

22. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

23. Claims 1, 3, 4, 9, 11, 12, 14, 17, 18, 20, 22, 23, 24, 25, and 27 are rejected under 35 U.S.C. 102(b) as being anticipated by Faustinella et al. in light of Panganiban '84 and Scarpa et al.

Claim 1 is drawn to a retroviral vector comprising a substitution of a portion of the 3' U3 region with a polylinker. Claim 3 is drawn to the vector of claim 1 further limited to a polylinker with a unique restriction site. Claim 4 is drawn to the vector of claim 3 further limited to comprise within the polylinker a heterologous DNA fragment. Claim 9 is drawn to the retroviral vector of claim 1 further limited to an LTR derived from a virus selected from the group consisting of murine leukemia virus, mouse mammary tumor virus, Murine sarcoma virus, simian immunodeficiency virus, human immunodeficiency virus, human T cell leukemia virus, feline immunodeficiency virus, feline leukemia virus, bovine leukemia virus, and mason-pfizer monkey virus. Claim 11 is drawn to the retroviral vector of claim 1 further

limited to comprise a coding sequence consisting of marker genes, therapeutic genes, antiviral genes, antitumor genes, or cytokine genes. Claim 12 is drawn to the vector of claim 11 further limited to a marker or therapeutic gene selected from the group consisting of beta-galactosidase gene, neomycin gene, Herpes Simplex Virus thymidine kinase gene, puromycin gene, cytosine deaminase gene, hygromycin gene, secreted alkaline phosphatase gene, guanine phosphoribosyl transferase gene, alcohol dehydrogenase gene, and hypoxanthine phosphoribosyl transferase gene. Claim 14 is drawn to the vector of claim 1 further limited to a vector in which sequences involved in integration are altered. Claim 17 is drawn to a kit comprising the retroviral vector of claim 1 and a packaging cell line that packages the vector of claim 1. Claim 18 is drawn to the kit of claim 17 further limited to a packaging cell line that expresses retroviral proteins not expressed by the vector of the kit. Claim 20 is drawn to a method of introducing nucleotide sequences by infection with the retroviral vector of claim 17 in human or animal cells in vitro or in vivo. Claim 22 is drawn to a retrovirus produced by the kit of claim 17. Claim 23 is drawn to a retroviral provirus produced by infecting cells with the retrovirus of claim 22. Claim 24 is drawn to mRNA of the provirus of claim 23. Claim 25 is drawn to RNA of the retrovirus of claim 1. Claim 27 is drawn to a method of introducing nucleotide sequences by infection with the retroviral vector of claim 22 in human or animal cells or cultured cells of a human or an animal.

Faustinella et al. shows in figure 1 Moloney murine leukemia retroviral vector pS3. pS3 comprises a partial deletion of the 3' U3 region, into which has been inserted a polylinker

with unique cloning sites, for example the Bsa AI site and the Nae I site used to construct the vectors of figure 2. pS3 also comprises a stop codon in the gag region. In figure 2, Faustinella et al. shows modified pS3 vectors in which the luciferase reporter gene operably linked to a rous sarcoma virus promoter or the hygromycin resistance gene operably linked to a herpes simplex thymidine kinase promoter has been inserted in the polylinker region. The luciferase gene is a well known marker gene and the thymidine kinase gene is a well known antitumor gene. Faustinella et al. shows in the Materials and Methods section that the viral vectors were packaged in the GP+AM12 cell line, which inherently expresses retroviral proteins not expressed by the retroviral vector, such as the gag protein, in its function as a packaging cell line. It is considered inherent that the packaging procedure as well as the expression of pS3 in NIH-3T3 cells detailed in Faustinella et al. shows the mRNA and RNA of the retroviral vector were produced during infection of cultured animal cells. Scarpa et al. shows in figure 2 and the discussion on page 851 that the mutation of the start codon in the gag region to a stop codon in pS3 results in the absence in translation of the pol gene. Panganiban '84 shows that the 3' end of the pol gene encodes the int locus that is required for integration of the reverse transcribed retroviral genome to form a provirus. Therefore, the stop codon mutation in pS3 affects sequences involved in the integration of retroviruses.

Therefore, Faustinella et al. anticipates the claimed invention.

*Claim Rejections - 35 USC § 103*

24. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

25. Claims 1, 3-9, 16, 17, and 19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Faustinella et al. in view of Couture et al. in view of Mee et al.

Claim 1 is drawn to a retroviral vector comprising a substitution of a portion of the 3' U3 region with a polylinker. Claim 3 is drawn to the vector of claim 1 further limited to a polylinker with a unique restriction site. Claim 4 is drawn to the vector of claim 3 further limited to comprise within the polylinker a heterologous DNA fragment. Claim 5 is drawn to the retroviral vector of claim 4 further limited to a heterologous DNA fragment that is a

regulatory element or a promoter. Claim 6 is drawn to the vector or claim 5 further limited to regulatory elements or promoters that are target cell specific. Claim 7 is drawn to the vector of claim 6 further limited to a target sell specific regulatory element and promoter selected from the group consisting of Whey Acidic Protein specific regulatory elements and promoters, Mouse Mammary Tumor Virus specific regulatory elements and promoters. beta lactoglobulin and casein specific regulatory elements and promoters, pancreas specific regulatory elements and promoters, lymphocyte specific regulatory elements and promoters, and mouse mammary tumor virus specific regulatory elements and promoters conferring responsiveness to glucocorticoid hormones or directing expression to the mammary gland. Claim 8 is drawn to the vector of claim 5 further limited to regulatory elements and promoters that regulate the expression of a coding sequence of the vector. Claim 9 is drawn to the retroviral vector of claim 1 further limited to an LTR derived from a virus selected from the group consisting of murine leukemia virus, mouse mammary tumor virus, Murine sarcoma virus, simian immunodeficiency virus, human immunodeficiency virus, human T cell leukemia virus, feline immunodeficiency virus, feline leukemia virus, bovine leukemia virus, and mason-pfizer monkey virus. Claim 16 is drawn to the vector of claim 5 further limited to regulatory elements regulatable by trans acting molecules. Claim 17 is drawn to a kit comprising the retroviral vector of claim 1 and a packaging cell line that packages the vector of claim 1. Claim 19 is drawn to the kit of claim 17 further limited to a packaging cell selected from the group consisting of psi-2, psi-crypt, psi-AM, GP+E86, PA317, and GP+envAM-12.

Faustinella et al. shows in figure 1 Moloney murine leukemia retroviral vector pS3. pS3 comprises a partial deletion of the 3' U3 region, into which has been inserted a polylinker with unique cloning sites, for example the Bsa AI site and theNae I site used to construct the vectors of figure 2. pS3 also comprises a stop codon in the gag region. In figure 2, Faustinella et al. shows modified pS3 vectors in which the luciferase reporter gene operably linked to a rous sarcoma virus promoter or the hygromycin resistance gene operably linked to a herpes simplex thymidine kinase promoter has been inserted in the polylinker region. The luciferase gene is a well known marker gene and the thymidine kinase gene is a well known antitumor gene. Faustinella et al. shows in the Materials and Methods section that the viral vectors were packaged in the GP+AM12 cell line, which inherently expresses retroviral proteins not expressed by the retroviral vector, such as the gag protein, in its function as a packaging cell line. It is considered inherent that the packaging procedure as well as the expression of pS3 in NIH-3T3 cells detailed in Faustinella et al. shows the mRNA and RNA of the retroviral vector were produced during infection of cultured animal cells. Faustinella et al. does not show heterologous DNA consisting of regulatory elements and promoters recited in claims 5-8, or the long terminal repeat regions recited in claim 9 other than the murine leukemia LTR, or regulatable elements that are explicitly regulated by trans acting molecules, or the packaging cells of claim 19, or a BAG vector, or a pharmaceutical comprising a retroviral vector.

Couture et al. (Reference AS in the Form PTO-1449 filed 9/23/97) shows a retroviral vector comprising a substitution of a portion of the 3' U3 region with the corresponding region

of 5 murine retroviruses. Couture et al. shows in the abstract that after packaging the substituted U3 region appears at the 5' LTR and serves as a promoter for vector genes, and that different LTR constructs were preferentially expressed in specific cell types. Couture et al. state on page 670 that promoter suppression or interference may occur within retroviral vectors containing internal promoter elements. Couture et al. states on page 667 that retroviral vectors with target cell specificity have utility in gene therapy protocols. Couture et al. shows the use of packaging cell lines PA317 and GP&E86 on page 669.

Mee et al. shows a retroviral vector comprising a mouse mammary tumor virus LTR, and that the LTR expressed a gene after induction with dexamethasone. Mee et al. state on page 292 that their vector is a potentially powerful tool for the manipulation of gene expression in a variety of cell types.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to modify the vector of Faustinella et al. by use of the LTR regions of Mee et al. because Couture et al. show that insertion of a promoter region in a deleted 3' U3 region of a retroviral vector results in the expression of vector genes under the control of the inserted promoter in a cell type specific manner, and that internal promoters may not function properly in a retroviral vector, and that target cell specific retroviral vectors have utility in gene therapy protocols, and because Mee et al. show that their LTR promoter may be used to manipulate gene expression in a variety of cell types. It would have been further obvious to

use packaging cell lines PA317 and GP&E86 because Couture et al. shows that they may be used to package retroviral vectors.

26. Claims 1, 10, 11, and 12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Faustinella et al. in view of Price et al.

Claims 1, 11, and 12 have been summarized above. Claim 10 is drawn to the vector of claim 1 further limited to a vector based on a BAG vector.

Faustinella et al has been summarized above.

Price et al. shows a BAG retroviral vector comprising a beta galactosidase reporter gene, and that the vector can be used to identify cells and progeny of cells infected with the vector.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to modify the vector of Faustinella et al. by basing the construction on a BAG vector of Price et al. because Price et al shows that a vector with a beta-galactosidase reporter gene may be used to identify cells and progeny of cells infected with the vector.

27. Claims 1, 3, 4, 15, 17, 20, 21, 22 26, and 27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Faustinella et al. in view of Longmore et al. and Kay et al.

Claims 1, 3, 4, 17, 20, 22, and 27 have been summarized above. Claim 15 is drawn to the vector of claim 4 comprising a DNA fragment homologous to a cellular sequence. Claim 26 is drawn to a pharmaceutical comprising the retrovirus of claim 22.

Faustinella et al. has been summarized above.

Longmore et al show in the abstract that mice infected with a retroviral vector expressing the erythropoietin receptor had increased platelet counts and splenic megakaryocytes.

Kay et al. shows in the abstract and throughout that hemophiliac dogs infected with a retroviral vector expressing factor IX shows improved levels of clotting and thromboplastin times for greater than 5 months after treatment.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to modify the vector of Faustinella et al. to express a therapeutic protein because both Kay et al. and Longmore et al. show that retroviral vectors may be used to express therapeutically effective levels of a recombinant protein in an animal.

***Conclusion***

28. Certain papers related to this application may be submitted to Art Unit 1636 by facsimile transmission. For routine submissions the FAX number is (703) 308-4242. For FAX transmissions in cases in which the Examiner has been notified by phone to expect the transmission, the FAX number is (703) 308-7939. In such cases please call the Examiner at (703) 308-4231 at the time of transmission to expedite delivery of the fax. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6 (d)). NOTE: If applicant *does* submit a paper by FAX, the original copy should be retained by applicant or

applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to John S. Brusca, Ph.D. whose telephone number is (703) 308-4231. The examiner can normally be reached on Monday through Friday from 9 AM to 5 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, George Elliott, Ph.D., can be reached at (703) 308-4003.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

John S. Brusca, Ph.D.

Examiner